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(54) Title: PROCESS FOR THE PREPARATION OF ROSIGLITAZONE MALEATE

(57) Abstract: The invention discloses a process for the preparation of a pyridine derivative namely 5-{4-2(N-methyl-N(2-pyridyl) amino ethoxy} benzyl] benzyl] thiazolidine 2,4-dione maleate comprising the steps of: a) reacting 2-chloropyridine with 2-(N-methyl amino) ethanol; b) coupling 2-(N-methyl-N-(2-pyridyl) amino) ethanol) obtained in step (a) and 4- fluorobenzaldehyde in an aproptic polar solvent with an alkali metal hydroxide or an alkali metal alkoxide as base; c) isolating the product of the coupling reaction viz 4-[2- (N-methyl-N-(2-pyridyl) amino) ethoxy] benzaldehyde; d) converting said isolated benzaldehyde compound of step (c) into 5-[4-[2-N-methyl-N-(2-pyridyl) amino)ethoxy] benzyl] thiazolidine 2,4-dione in a known manner and e) converting said thiazolidine 2,4-dione compound obtained in step (d) into a pharmaceutically acceptable maleate salt.

PROCESS FOR THE PREPARATION OF ROSIGLITAZONE MALEATE

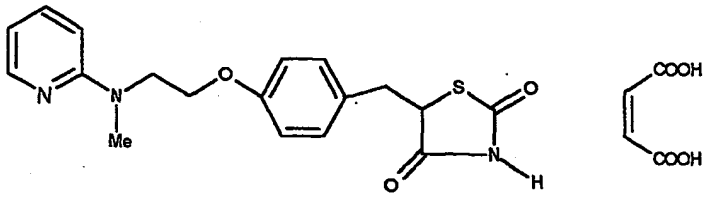
FIELD OF THE INVENTION

The present invention relates to a process for the preparation of 5- [4- [2- (N-methyl -N- (2- pyridyl) amino) ethoxy] benzyl] thiazolidine -2,4- dione maleate, namely, rosiglitazone maleate, the antidiabetic compound, which is the preferred drug for non-insulin dependent diabetes mellitus (NIDDM).

BACKGROUND OF THE INVENTION

Diabetes mellitus is a complex, chronically, progressive disease, which can eventually adversely affect the functioning of the kidneys, eyes, nervous and vascular systems. Most individuals diagnosed with diabetes mellitus show symptoms for non insulin dependent diabetes mellitus (NIDDM) that is, Type II diabetes. Type II diabetes is a debilitating disease that arises from improper energy storage and utilization. Type II diabetes is defined by high plasma glucose levels and is characterized by both peripheral insulin resistance and insufficient insulin secretion by the β-cells of the pancreas. The current approach for handling hyperglycemia is to alleviate insulin resistance rather than to stimulate insulin secretion. The thiazolidinedione class of antidiabetics such as pioglitazone, englitazone, troglitazone and ciglitazone have been shown to alleviate insulin resistance in humans.

Rosiglitazone maleate that is 5- [4- [2- (N- methyl -N- (2-pyridyl) amino) ethoxy] benzyl] thiazolidine -2,4- dione maleate of formula (I),



(I)

is a member of thiazolidinedione class and is one of the most potent compounds of this class, with a minimally effective dose of 3 μmol/kg diet. The comparative activity data for the various thiazolidinediones which are all being clinically progressed is summarized below :

Drug	Minimum effective dose (μmol/kg diet)
Rosiglitazone	3
Pioglitazone	200
Englitazone	200
Troglitazone	600
Ciglitazone	3000

Since, rosiglitazone is the preferred drug for non- insulin dependent diabetes mellitus, hence, the process for its production, yield obtained and costs involved are all constantly being critically surveyed for optimization.

European patent application 0306228, describes the coupling reaction of 2-(N- methyl -N- (2- pyridyl) amino) ethanol with 4- fluorobenzaldehyde in the

presence of dimethyl formamide as solvent and sodium hydride as base, but no yield has been reported.

Cantello et. al. (J. Med. Chem. 1994, 37, 3977 -3985) have independently prepared rosiglitazone and reported a yield of 48% for the coupling reaction of 2-(N- methyl -N-(2- pyridyl) amino) ethanol with 4- fluorobenzaldehyde in the presence of dimethyl formamide as solvent and sodium hydride as base for the synthesis of 4- [2- (N- methyl -N- (2- pyridyl) amino) ethoxy] benzaldehyde when carried out at a room temperature.

Moreover, Cantello et. al. (Biorganic and Medicinal Chemistry Letters Vol.45, Page 1181 - 1184, 1994) have reported a yield of 72% when the same reaction was carried out at 80°C.

In the present invention a significantly higher yield of 88%, is obtained in the coupling reaction carried out at room temperature. The reagent used provides a significant increase in yield from 48% to 88% when compared to Cantello's room temperature reaction as also an increase in yield from 72% to 88% when compared to Cantello's reaction at 80°C.

In the final step for the formation of the pharmaceutically acceptable maleate salt, Cantello et. al. have reported a yield of 62% using methanol as solvent. Pool et al (WO94/05659) have disclosed the yield of the crude maleate salt as 87%. In the present invention, a higher yield of 90- 95% of the pure maleate salt is obtained using a different solvent.

SUMMARY OF THE INVENTION

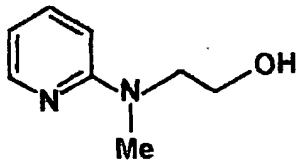
The object of the invention is to provide an improved process for the preparation of rosiglitazone maleate in high yield and high grade purity.

A further object of the invention is to provide 4- [2- (N- methyl -N- (2- pyridyl) amino) ethoxy] benzaldehyde in high yield by the coupling reaction of 2- (N- methyl -N- (2-pyridyl) amino) ethanol with 4- fluorobenzaldehyde.

Still another object of the invention is to provide the pharmaceutically acceptable salt, rosiglitazone maleate from rosiglitazone in high yield.

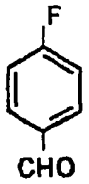
Accordingly, the present invention provides a process for the preparation of 5- [4- [2- (N- methyl -N- (2- pyridyl) amino) ethoxy] benzyl] thiazolidine -2,4- dione maleate, namely, rosiglitazone maleate of formula (I), which comprises the steps of:

a) reacting 2- chloropyridine with 2- (N- methyl amino) ethanol to yield the product alcohol 2- (N- methyl -N- (2- pyridyl)amino)ethanol (II);



(II)

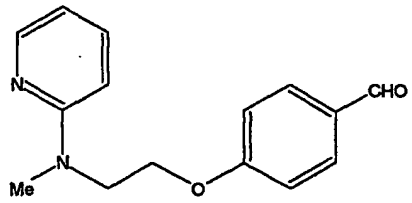
b) coupling 2- (N- methyl -N- (2- pyridyl) amino) ethanol (II) and 4- fluorobenzaldehyde (III)



(III)

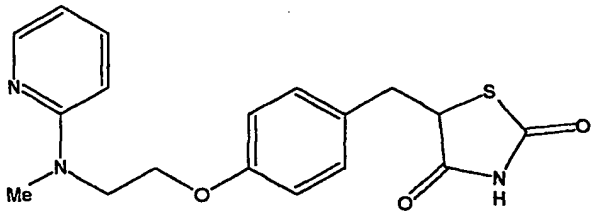
in an aprotic polar solvent with an alkali metal hydroxide or an alkali metal alkoxide as base;

c) isolating the product of the coupling reaction, namely 4- [2- (N- methyl -N- (2-pyridyl) amino) ethoxy] benzaldehyde (IV);



(IV)

d) converting said compound (IV) into 5- [4- [2-(N- methyl -N-(2- pyridyl) amino) ethoxy] benzyl] thiazolidine -2,4- dione (V) in a manner known per se, and

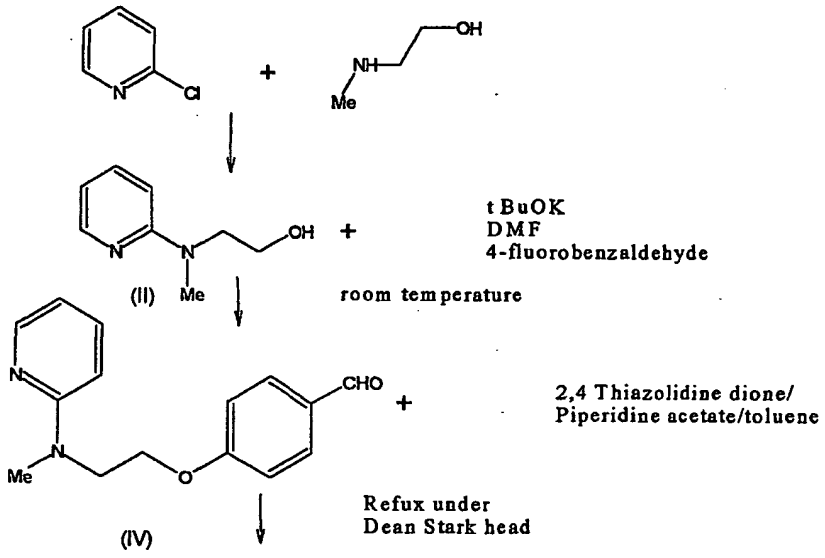


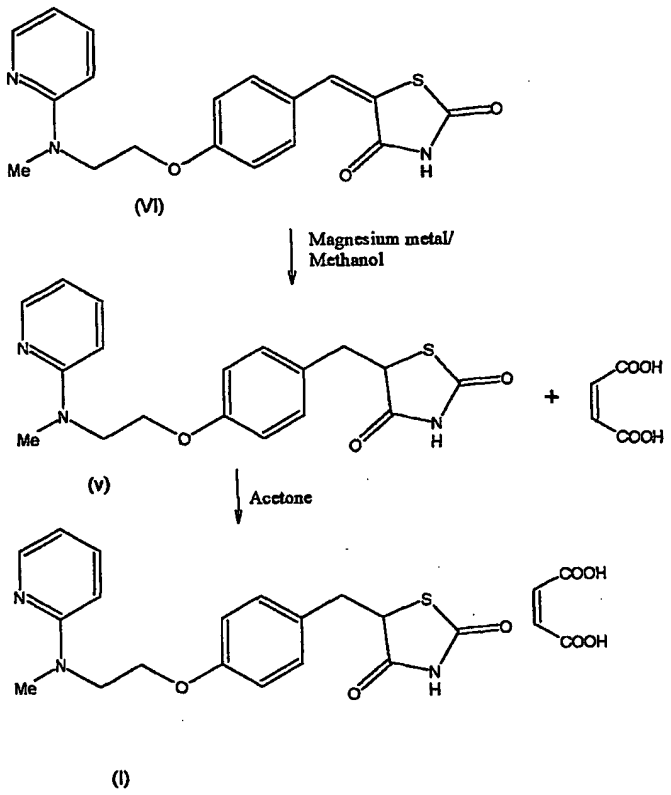
(V)

e) converting said compound (V) into its pharmaceutically acceptable maleate salt, 5- [4- [2- (N- methyl -N- (2- pyridyl) amino) ethoxy] benzyl] thiazolidine - 2,4- dione maleate (I), by reaction with maleic acid.

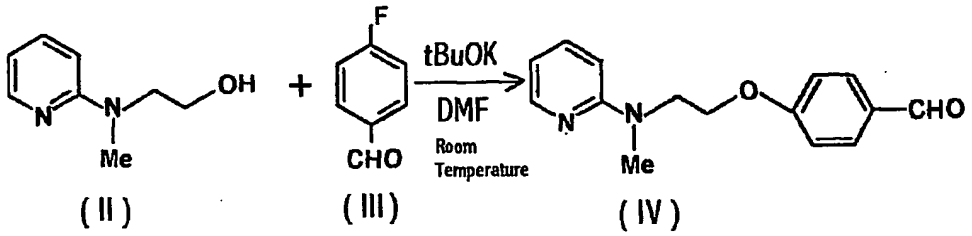
DETAILED DESCRITPION OF THE INVENTION

The synthetic route to the production of rosiglitazone maleate according to the present inventon is shown in the following scheme:





The reaction of 2- chloropyridine with 2- (N-methyl amino) ethanol provides 2- (N- methyl -N- (2- pyridyl) amino) ethanol (II), which on coupling reaction with 4-fluorobenzaldehyde (III) in an aprotic polar solvent with an alkali metal hydroxide or an alkali metal alkoxide as base yields 4- [2- (N- methyl -N- (2- pyridyl) amino) ethoxy] benzaldehyde (IV) with an 88% yield (Reaction I).



(II) (III) (IV)

Reaction - 1

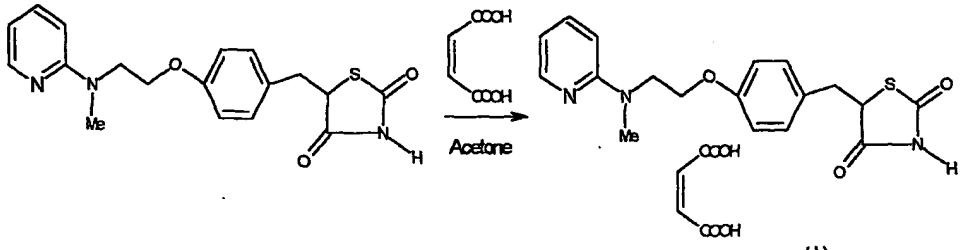
The preferred alkali metal is sodium or potassium and the alkoxide is of a lower alcohol (having C_1 to C_6) carbon atoms. Preferred alkali metal alkoxide is sodium methoxide and potassium tertiary butoxide and the most preferred alkali metal alkoxide is potassium tertiary butoxide. Further, the preferred alkali metal hydroxide is potassium hydroxide.

The reaction may be carried out in an aprotic polar solvent selected from the group dimethyl sulphoxide, dimethyl formamide and tetrahydrofuran, or mixtures thereof.

4- [2- (N- methyl -N- (2- pyridyl) amino) ethoxy] benzaldehyde (IV) was converted into 5- [4-[2-(N- methyl -N-(2-pyridyl) amino) ethoxy] benzyl] thiazolidine -2,4- dione (V), namely, rosiglitazone, in a manner known per se, by Knoevenegal condensation with 2,4- thiazolidinedione, to give the highly crystalline benzylidene derivative (VI), in 95% yield and the subsequent reduction of the double bond with magnesium metal in methanol to obtain rosiglitazone (V) in 72% yield.

In the final step of salt formation, rosiglitazone (V) and maleic acid were refluxed in acetone at 50°to 55°C to obtain the maleate salt 5- [4-[2-(N- methyl - N- (2- pyridyl) amino) ethoxy] benzyl] thiazolidine -2,4- dione maleate (I), namely rosiglitazone maleate in high yield of 90 to 95% with high grade purity and low

moisture content to be effectively dry and free flowing so that it can easily be converted into a pharmaceutical composition.



(V) (I)

REACTION-2

The degree of purity of Rosiglitazone maleate (bulk drug) synthesized according to the instant process is substantially high with the impurity level less than 0.1%. In fact the impurity level is so small that as per current USFDA Standard and other international regulations, no further analysis of the impurity is required. This level of purity has been possible to achieve by following the process steps according to the instant invention.

Acetone can also be easily and effectively removed compared to the alcoholic solvent methanol which was used in prior art process.

The following procedures and examples illustrate the invention but do not limit it in anyway.

EXAMPLE

Preparation of 4 - [2- (N- methyl -N- (2- pyridyl) amino) ethoxy] benzaldehyde (IV):

In a 2ℓ three necked, round bottom flask, 500 ml dimethylformamide is added, followed by addition of 100g of 2- (N- methyl -N- (2- pyridyl) amino) ethanol (II)

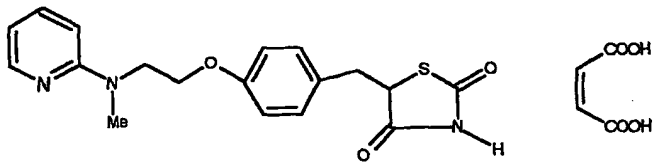
and 100 g of 4- fluorobenzaldehyde (III) was added to the reaction mixture and it was stirred for 10 minutes at room temperature and 80g of potassium tertiary butoxide was added to the reaction mixture. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to 5 - 10°C and under the cold conditions, 1.5ℓ of water was added and stirred for 15 min. The mixture was extracted with 4 x 500 ml of ethyl acetate. The combined organic layer was washed with 3 x 1ℓ water. The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to give 148 g (88 %) of 4- [2- (N- methyl -N- (2- pyridyl) amino) ethoxy] benzaldehyde (IV).

Preparation of 5 -[4-[2-(N- methyl -N- (2- pyridyl) amino) ethoxy] benzyl] thiazolidine -2,4- dione maleate (I):

800 g of 5- [4-[2- (N- methyl -N- (2- pyridyl) amino) ethoxy] benzyl] thiazolidine -2,4- dione (V) and 280 mg maleic acid were dissolved in 1.3ℓ of acetone in 5ℓ three necked round bottom flask. The reaction mixture was heated to 50°- 55°C and the solution was filtered and slowly cooled to obtain 986 g of 5-[4-[2-(N- methyl -N- (2-pyridyl) amino) ethoxy] benzyl] thiazolidine -2,4- dione maleate (I) (yield 95%; mp 120-122°C).

I CLAIM:

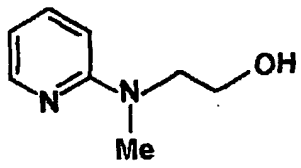
1. A process for the preparation of 5- [4-[2-(N- methyl -N-(2- pyridyl) amino) ethoxy] benzyl] thiazolidine -2,4- dione maleate, namely, rosiglitazone maleate of formula (I),



(I)

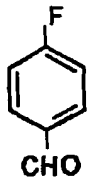
which comprises the steps of:

a) reacting 2- chloropyridine with 2- (N- methyl amino ethanol to yield the product alcohol 2- (N- methyl -N- (2- pyridyl) amino) ethanol (II);



(II)

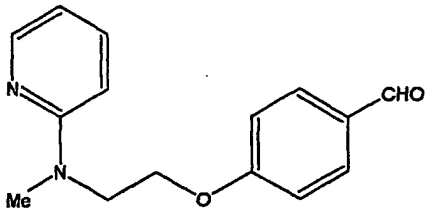
b) coupling 2- (N- methyl -N- (2- pyridyl) amino) ethanol (II) and 4- fluorobenzaldehyde (III)



(III)

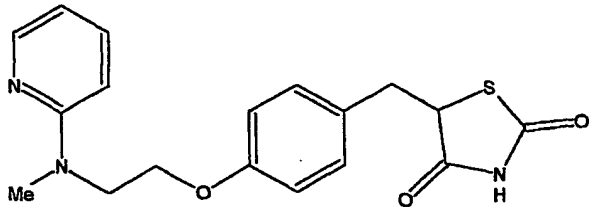
in an aprotic polar solvent with an alkali metal hydroxide or an alkali metal alkoxide as base at a temperature range of 25° to 30°C.

c) isolating the product of the coupling reaction, namely, 4- [2- (N-methyl - N- (2- pyridyl) amino) ethoxy] Benzaldehyde (IV);



(IV)

d) converting said compound (IV) into 5- [4-[2-(N- methyl-N- (2- pyridyl) amino) ethoxy] benzyl] thiazolidine -2,4-dione (V) in a manner known per se; and



(V)

e) converting compound (V) into its pharmaceutically acceptable maleate salt, 5- [4-[2-(N- methyl -N- (2- pyridyl) amino) ethoxy] benzyl] thiazolidine -2,4-dione maleate (I), by reaction with maleic acid.

2. A process as claimed in claim 1, wherein said alkali metal is sodium or potassium.

3. A process as claimed in claim 1, wherein said alkoxide is of a lower alcohol having C_1 to C_6 carbon atoms.

4. A process as claimed in claim 1, wherein said alkali metal alkoxide is selected from amongst sodium methoxide and potassium tertiary butoxide.

5. A process as claimed in claim 4, wherein said alkali metal alkoxide is potassium tertiary butoxide.

6. A process as claimed in claim 1, wherein said alkali metal hydroxide is potassium hydroxide.

7. A process as claimed in claim 1, wherein the reaction temperature in step (b) is room temperature.

8. A process as claimed in claim 1, wherein the solvent used for the conversion step (e) is acetone.

9. A process as claimed in claim 1, wherein the reaction temperature in step (e) is 50 to 55°C.

10. A process for the preparation of 5- [4-[2-(N- methyl -N-(2- pyridyl) amino) ethoxy] benzyl] thiazolidine -2,4- dione maleate, namely, rosiglitazone maleate of formula (I), substantially as herein described particularly with reference to the foregoing example.

INTERNATIONAL SEARCH REPORT

ıtional Application No
PCT/IB 01/01367

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D277/34 //C07D213/74

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, EPO-Internal, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	CHEMICAL ABSTRACTS, vol. 134, no. 20, 14 May 2001 (2001-05-14) Columbus, Ohio, US; abstract no. 280683k, LI J ET AL: "Improved method for the synthesis of 4-'2-(methyl-2-pyridinylamino)ethoxy! benzaldehyde" page 684; XP002187086 abstract & HUAXUE SHIJI, vol. 22, no. 6, 2000, page 372 -/—	1-9

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 January 2002	25/01/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Allard, M

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	CANTELLO B C C ET AL: "'Omega-(Heterocyclylamino)alkoxy!benzyl! -2,4-thiazolidinediones as potent antihyperglycemic agents" JOURNAL OF MEDICINAL CHEMISTRY, vol. 37, no. 23, 1994, pages 3977-3985, XP002127022 cited in the application the whole document, particularly page 3978, scheme 3, reaction b, and page 3981, right-hand column, last paragraph	1-9
Y	CANTELLO B C C ET AL: "The synthesis of BRL 49653 - a novel and potent antihyperglycaemic agent" BIOORGANIC & MEDICINAL CHEMISTRY, vol. 3, no. 10, 1994, pages 1181-1184, XP001052838 cited in the application the whole document	1-9
Y	ABARBRI M ET AL: "Les beta-cétonitriles groupes protecteurs de la fonction amine. Préparation d'amino-alcools" HELVETICA CHIMICA ACTA, vol. 78, no. 1, 8 February 1995 (1995-02-08), pages 109-121, XP002187084 the whole document, particularly page 120, preparation of 2n	1-9
Y	REDDY K A ET AL: "Novel antidiabetic and hypolipidemic agents. 5. Hydroxyl versus benzyloxy containing chroman derivatives" JOURNAL OF MEDICINAL CHEMISTRY, vol. 42, no. 17, 26 August 1999 (1999-08-26), pages 3265-3278, XP002187085 the whole document, particularly page 3267, scheme 3, (13) -> (16), same page, left-hand column, last paragraph, paragraph bridging pages 3272 and 3273, and page 3275, right-hand column, preparation of (16)	1-9
P,X	WO 01 44240 A (RICHTER GEDEON VEGYÉSZETI GYÁR RT.) 21 June 2001 (2001-06-21) the whole document	1-9

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 10

The scope of claim 10 is so unclear (Article 6 PCT) that a meaningful international search is impossible with regard to this claim.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

tional Application No
PCT/IB 01/01367

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0144240 A	21-06-2001	AU 2210401 A	25-06-2001
		WO 0144240 A1	21-06-2001